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(54) Pyrimidine derivatives as HMG-CoA reductase inhibitors

Pyrimidinderivate als HMG-CoA reduktase Hemmer

Dérivés de pyrimidine comme inhibiteurs de la HMG-CoA reductase

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Description

[0001] The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors

[0002] The first generation of drags for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, are mevinolin (U.S.Pat. No.4,231,938), pravastatin sodium (U.S. Pat.No.4,346,227), and simvastatin (U.S.Pat.No.4,444,784), which are fungal metabolites or chemical derivatives thereof. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (F.G.Kathawala et al, 8th Int'l Symp. on Atherosclerosis, Abstract Papers, p.445, Rome (1988)) and BMY 22089 (GB Pat.No.2,202,846) were developed as the second generation drags.

[0003] The compounds of the present invention inhibit the HMG-CoA reductase, which plays a major role in the synthesis of cholesterol, and thus they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

[0004] The present invention relates to (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl sulfonyl amino) pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid or a non-toxic pharmaceutically acceptable salt thereof.

[0005] This invention also provides a pharmaceutical composition comprising the same as well as a process for preparing the same.

[0006] In the specification, the term "lower alkyl" refers to a straight, branched, or cyclic C_1 to C_6 alkyl, including methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, cyclopentyl, n-hexyl, and isohexyl and the like. Further, the lower alkyl may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano. Halogen means fluorine, chlorine, bromine and iodine.

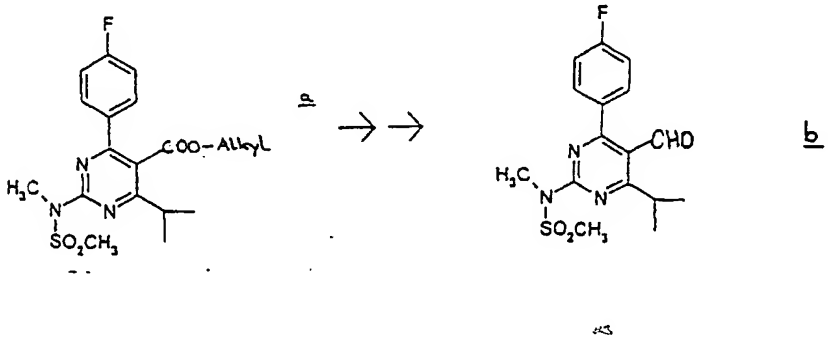
[0007] The term "a non-toxic pharmaceutically acceptable salt" refers to a salt in which the cation is an alkali metal ion, an alkaline earth metal ion, or an ammonium ion. Examples of alkali metals are lithium, sodium, potassium, and cesium, and examples of alkaline earth metals are beryllium, magnesium, and calcium. Sodium and calcium are preferred.

[0008] The compounds of the present invention can be prepared by the following method.

[0009] (1) The carboxylate group of the compound a is converted into the alcohol group by reduction in an appropriate inactive solvent such as THF, ether, and toluene in the presence of a reductant such as $LiAlH_4$ and DIBAL-H. The reaction is performed at -70 to 50 °C, preferably at around room temperature, for 10 minutes to 10 hours, preferably for 30 minutes to 3 hours. Then the obtained alcohol is subjected to oxidation in an appropriate solvent such as methylene chloride in the presence of the oxidizing agent such as TPAP/4-methylmorpholin-N-oxide or pyridium chlorochromate to give the aldehyde compound b. The reaction is performed at 0-60 °C, preferably at around room temperature, for 10 minutes to 10 hours, preferably 30 minutes to 3 hours.

Compounds a and b have the following structure:

[0010]



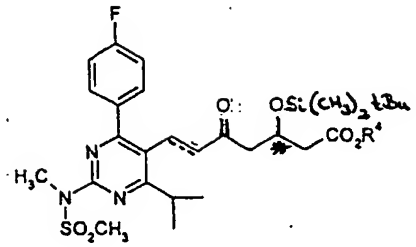
[0011] wherein

Alkyl means lower alkyl.

[0012] (2) The obtained compound b is subjected to reaction with (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanoic acid derivatives in an appropriate solvent such as acetonitrile, diethylether, tetrahydrofuran, and dimethylformamide to give the compound c. The reaction is performed for 1-30 hours preferably for 10-15 hours under heating.

Compound c has the following structure:

[0013]



c

wherein C* represents an asymmetric carbon atom, the dotted line denotes the presence of the double bond and R^4 is a lower alkyl.

[0014] (3) The compound c is subjected to elimination of the tert-butyldimethylsilyl group in an appropriate organic solvent in the presence of a hydrogen halogenide to give the compound d.

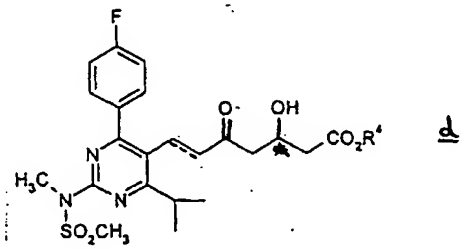
[0015] Every sort of halogen can be used for hydrogen halogenide. Amongst all, hydrogen fluoride is preferred.

[0016] The same organic solvents as used in the step (2) may be employed. Acetonitrile is especially preferred.

[0017] The reaction is performed in a range of from 0 to 60 °C, preferably at room temperature, for 0.5-10 hours, preferably for 1-2 hours.

Compound d has the following structure:

[0018]



d

wherein C*, the dotted line and R^4 each have the same meaning as defined above.

[0019] (4) The compound d is reacted with diethylmethoxyborane and $NaBH_4$ in an alcohol-organic solvent mixture and subjected to column chromatography on silica gel.

[0020] The reaction is performed at a temperature between -100 to 20 °C, preferably between -85 to -70 °C under cooling for 10 minutes to 5 hours, preferably for 30 minutes to 2 hours.

[0021] Here, the alcohol includes methanol, ethanol, propanol, and butanol; and the organic solvent includes the same as in the step (3).

[0022] Further, the obtained compound is subjected to saponification with a solution of metallic hydroxide (when the desired product is a non-toxic pharmaceutically acceptable salt); after the saponification, the reaction mixture may be neutralized with an acid and extracted with an organic solvent (when the desired product is the free acid). The saponification is performed in a polar solvent such as water, acetonitrile, dioxane, acetone, or a mixture thereof, preferably in the presence of a base, by a conventional method. The reaction is performed at 0 to 50 °C, preferably at around room temperature.

[0023] As the metallic hydroxide sodium hydroxide, potassium hydroxide, and their analogues may be used.

[0024] Acids which may be used include inorganic acids such as hydrochloric acid, sulfuric acid and the like.

[0025] Further, if necessary, the obtained compounds are subjected to reflux under heating to give the corresponding lactones.

[0026] Pharmaceutical compositions comprising the compounds of the present invention can be administered orally or parenterally. For example, the compound of the present invention may be orally administered in the form of tablets, powders, capsules, and granules, aqueous or oily suspension, or liquid form such as syrup or elixir, and parenter-

ally in the form of aqueous or oily suspension.

[0027] These preparations can be prepared in a conventional manner by using excipients, binders, lubricants, aqueous or oily solubilizers, emulsifiers, suspending agents, and the like. Preservatives and stabilizers can be also used.

[0028] The dosages may vary with the administration route, age, weight, condition, and the kind of disease of the patients, but are usually 0.5-200 mg/day, preferably 1-100 mg/day for oral administration and 0.1-100 mg/day, preferably 0.5-50 mg/day for parenteral administration. They may be used in single or divided doses.

[0029] The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

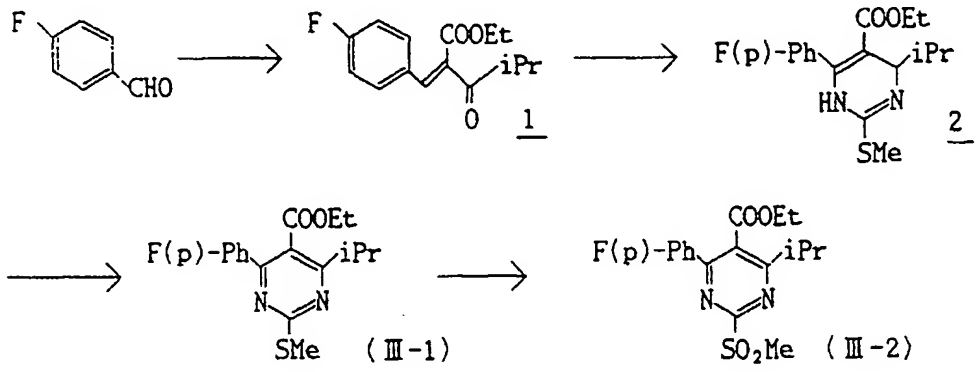
[0030] The abbreviations used in examples and reference examples have the following meanings.

Me : methyl, Et : ethyl, i-Pr : isopropyl
t-Bu : tert-butyl, Ph : phenyl,
DMF : dimethylformamide, THF : tetrahydrofuran
DDQ : 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
TPAP : tetrapropylammonium perruthenate
HMPA : hexamethylphosphoramide
DIBAL-H : diisobutylaluminum hydride

Reference Example 1

Ethyl 4- (4-fluorophenyl) -6-isopropyl-2-methylthiopyrimidine-5-carboxylate (III-1) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonylpyrimidine-5-carboxylate (III-2)

[0031]



[0032] p-Fluorobenzaldehyde (81.81) g is reacted in the same manner as disclosed in the specification of JP Unexamed. Pat. Publn. No.61-40272 to give 151.0 g (Yield : 86.7 %) of the compound 1. Then the mixture of a solution of 44.68 g of the compound 1 in 65 ml of HMPA and 28.24 g of s-methylisourea hydrogen sulfate is stirred at 100 °C for 22 hours. Then the reaction mixture is extracted with ether, and washed with saturated sodium hydrogencarbonate and then with water. The organic layer is dried, and the solvent is distilled away. The obtained residue is subjected to column chromatography on silica gel to give 26.61 g (yield : 46.8%) of the compound 2.

[0033] To a solution of the obtained compound 2 in 400 ml of benzene 21.64 g (0.095 mmol) of DDQ is added and the mixture is stirred for 30 minutes. Then the mixture is subjected to column chromatography on silica gel to give 24.31 g (Yield : 91.9 %) of the compound (III-1).

NMR ($CDCl_3$) δ :
1.10 (t, J=7,3H); 1.31 (d, J=7,6Hz); 2.61 (s, 3H); 3.18 (hept, J=7,1H); 4.18 (q, J=7,2H); 7.12 (m, 2H); 7.65 (m, 2H)

[0034] To a solution of 13.28 g (0.04 mmol) of the compound (III-1) in chloroform 17.98 g of m-chloroperbenzoic

acid is added and the reaction mixture is stirred at room temperature. Then it is washed with sodium sulfate and then with saturated sodium hydrogencarbonate. The solution is dried, and the solvent is distilled away and washed with n-hexane to give 13.93 g (Yield : 95.7%) of the compound (III-2).

NMR ($CDCl_3$) δ :
1.16 (t, J=7,3H); 1.37 (d, J=7,6H); 3.26 (hept, J=7,1H); 3.42 (s, 3H); 4.28 (q, 2H); 7.18 (m, 2H); 7.76 (m, 2H)

Reference Example 2

Another synthetic method of the compound (III-1)

[0035] To a solution of 200 mg (0.594 mmol) of the compound 2 in 5 ml of dichloromethane 0.5 g (6.10 equivalent) of potassium carbonic anhydride is added and 166 mg (1.1 equivalent) of iodine, and the mixture is stirred at room temperature for 2.5 hours. After the reaction, saturated sodium hydrogensulfite is added to the mixture which is then extracted with ether. The organic layer is washed with water and dried. The solvent is distilled off under reduced pressure to give 166 mg (Yield : 83.6%) of the compound (III-1) as resinous substance. NMR ($CDCl_3$) δ : 1.10 (t, 3H, J=7); 1.31 (d, 6H, J=7); 2.61 (s, 3H); 3.17 (heptet, 1H, J=7); 4.18 (q, 2H, J=7); 7.07-7.17 (m, 2H); 7.61-7.69 (m, 2H)

Reference Example 3

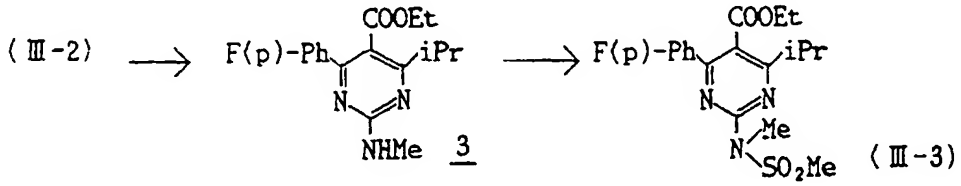
Another synthetic method of the compound (III-2)

[0036] To a solution of 1.0 g (2.97 mmol) of the compound 2 in 10 ml of acetone 1.5 g (9.48 mmol) of potassium permaganate is added and the mixture is stirred at room temperature for 15 minutes. Acetic acid (1.0 ml) is added thereto, and the mixture is stirred at room temperature for further 30 minutes and water is added thereto. The reaction mixture is extracted with ether, washed with saturated sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent is distilled away under redueced pressure to give 1.07 g (2.94 mmol) (Yield : 99.1 %) of the compound (III-2) as crystals.

Reference Example 4

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-carboxylate (III-3)

[0037]



[0038] To a solution of 52.7 g (144 mmol) of the compound (III-2) in 500 ml of absolute ethanol solution of 71.9 ml of 5N methylamine in ethanol is added gradually under ice-cooling. The reaction mixture is warmed to room temperature, stirred for 1 hour and evaporated under reduced pressure. To the residue water is added and the mixture is extracted with ether, dried and evaporated under reduced pressure to give 46.9 g (Yield : 100%) of the compound 3.
mp. 85-86°C

Anal Calcd. (%) for $C_{17}H_{20}N_3FO_2$				
	C,64.34;	H,6.35;	N,13.24;	F,5.99

(continued)

Anal Calcd. (%) for $C_{17}H_{20}N_3FO_2$				
Found	C,64.42;	H,6.46;	N,13.30;	F,6.14

[0039] To a solution of 370 mg (1.213 mmol) of the compound 3 in 5 ml of DMF 60 mg of 60% NaH is added under ice-cooling and the reaction mixture is stirred for 30 minutes. Methanesulfonyl chloride 208 mg is added thereto, and the mixture is warmed to room temperature and stirred for 2 further hours. To the mixture ice-water is added and the mixture is extracted with ether. The organic layer is washed with water and dried. The solvent is evaporated under reduced pressure, and the resulting residue is washed with ether-n-pentane to give 322 mg (Yield: 57.6%) of the compound (III-3).

NMR ($CDCl_3$) δ :
1.10 (t, J=7,3H); 1.32 (d, J=7,6H); 3.24 (hept, J=7,1H); 3.52 (s,3H); 3.60 (s, 3H); 4.19 (q, J=7,2H); 7.14 (m, 2H); 7.68 (m, 2H)

Reference Example 5

Methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate

[0040] (1) (3R)-3-(tert-butyldimethylsilyloxy)glutaric acid-1-((R)-(-)-mandelic acid ester*1 (65 g ,164 mmol) is dissolved in 60 ml of methanol. A solution of sodium methoxide in methanol (28% methanol 310 ml, 1.6 mol) is added dropwise thereto under a nitrogen atmosphere at 0°C for 45 minutes at an internal temperature under 7°C. The reaction mixture is stirred at 0°C for 30 minutes and poured into a mixture of 150 ml of conc.HCl, 300 ml of water, and 500 ml of methylene chloride being stirred under ice-cooling. The organic layer is collected. The aqueous layer is extracted with 200 ml of methylene chloride, and each organic layer is washed with dil.HCl and then with brine. Each organic layer is collected and dried over anhydrous magnesium sulfate and evaporated to distill off the solvent to give the half ester compound.

^{1}HNMR($CDCl_3$) δ :
0.08 (s, 3H); 0.09 (s, 3H); 0.86 (s, 9H); 2.52-2.73 (m, 4H); 3.08 (s, 3H); 4.55 (quint, 1H, J=6Hz)
IR ($CHCl_3$) : 2880, 1734, 1712, 1438, 1305, 1096, 836 cm^{-1}
[α]D=-5.0±0.4° (C=1.04, 23.5°C, $CHCl_3$)
Rf 0.32 ($CHCl_3$/MeOH=9/1)

[0041] (2) To a solution of the thus obtained half ester compound in 10 ml of ether triethylamine and then ethyl chlorocarboxylate are added dropwise under nitrogen atmosphere at -78°C. The resulting white suspension is stirred at 0 °C for 1 hour and cooled to -78 °C. The resulting precipitate is filtered off under nitrogen atmosphere and the filtrate is washed with 15 ml of ether. To a suspension of 1.29 g (3.6 mmol) of methyl bromide triphenylphosphonium in 5 ml of THF butyllithium (1.6M hexane, 2.25 ml, 3.6 mmol) is added dropwise under a nitrogen atmosphere at -78°C. The reaction mixture is stirred at 0°C for 1 hour and cooled to -78°C and added dropwise to the solution of the thus obtained active ester compound in ether. The reaction mixture is washed with 5 ml of THF and stirred at 0 °C for 1 hour, and 10 ml of 5 % sodium hydrogencarbonate is added thereto. The reaction mixture is stirred for 5 minutes and extracted with ethyl acetate and the organic layer is separated and the remaining aqueous layer is extracted with ethyl acetate. Each organic layer is collected and washed with brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue is subjected to column chromatography on silica gel eluting with ether-ethyl acetate and crystallized from ether-hexane to give the objective compound.

^{1}HNMR ($CDCl_3$) δ :
0.04 (s, 3H); 0.06 (s, 3H); 0.83 (s, 9H); 2.4-2.9 (m, 4H); 3.64 (s, 3H); 3.74 (d, 1H); 4.5-4.7 (m, 1H); 7.4-7.8 (m, 15H)
IR ($CHCl_3$) : 2880, 1730, 1528, 1437, 1250, 1106, 835 cm^{-1}
[α]D=-6.2° (C=1.27, 22.0°C, $CHCl_3$)
mp. :77.5-78.5°C, Rf=0.48 ($CHCl_3$/MeOH=9/1)

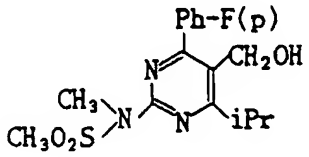
*1 This compound can be prepared by the method described on page 10 in the specification of KOKAI 2-250852.

Anal Calcd. (%) for $C_{31}H_{59}O_4PS$			
	C, 69.63;	H,7.35;	P,5.79
Found	C, 69.35;	H,7.35;	P,6.09

Example 1

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I a-1)

[0042] (1) To a solution of 322 mg of the compound (III-3) obtained in Reference Example 2 in 7 ml of anhydrous toluene 1.4 ml of DIBAL-H in 1.5M toluene is added dropwise at -74°C. The reaction mixture is stirred for 1 hour and acetic acid is added thereto. The mixture is extracted with ether. The organic layer is washed with sodium bicarbonate and water, dried and then evaporated under reduced pressure to distill off ether. The obtained residue is subjected to column chromatography on silica gel, eluting with methylene chloride/ether (20/1) to give 277 mg (Yield : 96.1%) of [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl-amino)pyrimidin-5-yl]methanol 4.



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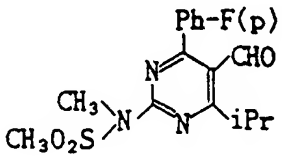
[0043] (2) A suspension of 277 mg of the thus obtained compound 4, 190 mg of 4-methylmorpholin-N-oxide, 6 mg of TPAP, 1.0 g of powder molecular sieve 4A, and 10 ml of methylene chloride is stirred for 2 hours. The insoluble matter is filtered off and two-thirds of the filtrate is distilled away under reduced pressure. The resulting residue is subjected to column chromatography on silica gel eluting with methylene chloride to give 196 mg (Yield : 71.2%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidinecarbaldehyde as crystals.



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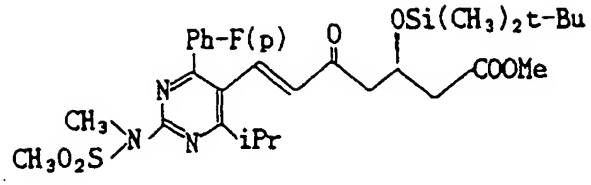
[0044] (3) A solution of 190 mg of the compound 5, 450 mg of methyl (3R) -3- (tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate (Reference Example 5), and 5 ml of acetonitrile is refluxed under heating for 14 hours and evaporated under reduced pressure to distill off acetonitrile. The resulting residue is subjected to column chromatography on silica gel eluting with methylene chloride to give 233 mg (Yield : 71.3%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl)-(3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-(E)-6-heptenate 6 as a syrup.



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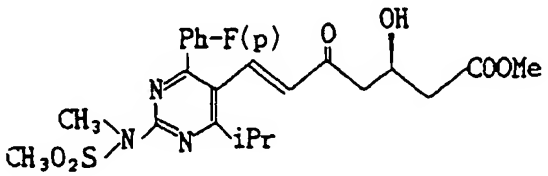
[0045] (4) To a solution of 16 g of the compound 6 in 100 ml of acetonitrile a solution of 48% hydrogen fluoride in 400 ml of acetonitrile (1:19) is added dropwise under ice-cooling, and the mixture is warmed to room temperature and stirred for 1.5 hours. The reaction mixture is neutralized with sodium bicarbonate and extracted with ether. The organic layer is washed with sodium chloride, dried and evaporated under reduced pressure to distill off ether to give 13 g (Yield : 100%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R)-3-hydroxy-5-oxo-(E)-6-heptenate 7 as a syrup.



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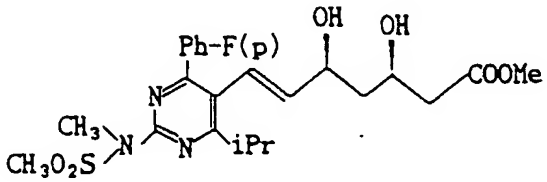
[0046] (5) To a solution of 13 g of the compound 7 in 350 ml of anhydrous THF and 90 ml of methanol a solution of 29.7 ml of 1M diethylmethoxyborane-THF is added at -78°C, and the mixture is stirred at the same temperature for 30 minutes. To the mixture 1.3 g of $NaBH_4$ is added and the mixture is stirred for 3 hours. Acetic acid (16 ml) is added thereto, and the mixture is adjusted to pH 8 with saturated sodium bicarbonate and extracted with ether. The organic layer is washed with water, dried and the ether is evaporated under reduced pressure. To the resulting residue methanol is added and the mixture is evaporated under reduced pressure for three times. The resulting residue is subjected to column chromatography on silica gel, eluting with methylene chloride/ether (3/1) to give 11.4 g (Yield : 85.2%) of methyl 7-[4-(4-fluorophenyl)-6-iso-propyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate as a syrup.

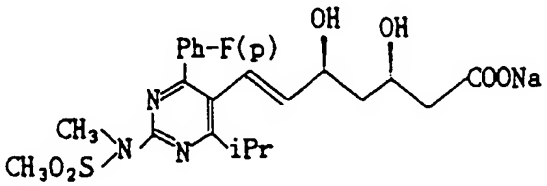


(Ib-1)

NMR ($CDCl_3$) δ :
1.27 (d, J=7,6H); 1.53 (m, 2H); 2.47 (d, J=6,2H); 3.36 (hept, J=2H); 3.52 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 4.20 (m, 1H); 4.43 (m, 1H); 5.45 (dd, J=5,16, 1H); 6.64 (dd, J=2,16, 1H); 7.09 (m, 2H); 7.64 (m, 2H)

[0047] (6) To a solution of 11.4 g of the compound (Ib-1) in 160 ml of ethanol 223 ml of 0.1 N sodium hydroxide is

added under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 1 hour. The solvent is distilled off under reduced pressure, and ether is added to the resulting residue and the mixture is stirred to give 11.0 g (Yield : 95.0%) of the objective compound (I a-1) as powdery crystals.



(I a-1)

$[\alpha]_D$=+18.9±0.6° (C=1.012, 25.0°C, H_2O)
NMR ($CDCl_3$) δ :
1.24 (d, J=7,6H); 1.48 (m, 1H); 1.65 (m, 1H); 2.27 (dd,J=2,6.2H); 3.41 (hept, J=7,1H); 3.48 (s, 3H); 3.59 (s, 3H); 3.73 (m, 1H); 4.32 (m, 1H); 5.49 (dd, J=7,16, 1H); 6.62 (d, J=16,1H); 7.19 (m, 2H); 7.56 (m, 2H)

Example 2

Calcium salt of the compound (I a-1)

[0048] The compound (I a-1) (sodium salt) 1.50 g (3.00 mmol) is dissolved in 15 ml of water and stirred at room temperature under a nitrogen atmosphere. Successively 3.00 ml (3.00 mmol) of 1 mol/L calcium chloride is added dropwise thereto over 3 minutes. The reaction mixture is stirred at the same temperature for 2 hours, and the resulting precipitate is collected, washed with water and dried to give 1.32 g of calcium salt as powder. This compound started to melt at a temperature of 155 °C, but the definitive melting point is ambiguous. [α]D=+6.3±0.2° (C=2.011, 25.0°C, MeOH)

Anal Calcd. (%) for $C_{22}H_{27}N_3O_6SF \cdot 0.5Ca \cdot 0.5H_2O$					
	C,51.85;	H,5.53;	N,8.25;	F,3.73;	Ca,3.93
Found	C,51.65;	H,5.51;	N,8.47;	F,3.74;	Ca,4.07

Biological Activity

Experiment

The HMG-CoA reductase inhibitory effect

(1) Preparation of rat liver microsomes

[0049] Sprague-Dawley rats, which were in free access to ordinary dietes containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsomes The thus obtained microsomes were then purified according to the manner described by Kuroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105000 × g was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down and kept at -80°C.

(2) Measurement of the HMG-CoA reductase inhibitory activities

[0050] The rat liver microsome sample (100 μ ℓ), which was preserved at -80 °C, was fused at 0°C and diluted with

0.7 ml of a cold potassium phosphate buffer (100 mM, pH7.4). This was mixed with 0.8 ml of 50 mM EDTA (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100 mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the mixture was kept at 0°C. The microsome solution (1.675 ml) was mixed with 670 μℓ of 25 mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to the solution of 0.5mM [3-^{14}C]HMG-CoA (3mCi/ mmol). A solution (5 μℓ) of sodium salt of the test compound dissolved in potassium phosphate buffer was added to 45 μℓ of the mixture. The resulting mixture was incubated at 37 °C for 30 minutes and cooled. After termination of the reaction by addition of 10 μℓ of 2N-HCl, the mixture was incubated again at 37 °C for 15 minutes and then 30 μℓ of this mixture was applied to thin-layer chromatography on silica gel of 0.5 mm in thickness (Merck AG, Art. 5744). The chromatograms were developed in toluene/acetone (1/1) and the spot, whose Rf value was between 0.45 to 0.60, were scraped. The obtained products were put into a vial containing 10 ml of scintillator to measure specific radio-activity with a scintillation counter. The activities of the present compounds are shown in Table 4 as comparative data, based on the assumption that the activity of mevinolin (sodium salt) as the reference drug is 100.

Table 4

Test Compound	HMG-CoA reductase inhibitory activities
I a-1	442
Mevinolin Na	100

[0051] The test data demonstrates that the compounds of the present invention exhibit HMG-CoA reductase inhibition activities superior to mevinolin.

Claims

1. The compound (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid or a non-toxic pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 which is (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid

3. A compound as claimed in claim 1 which is the calcium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

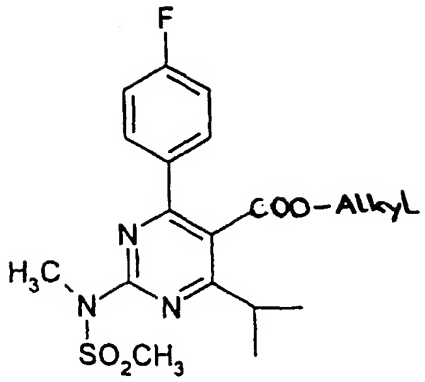
4. A compound as claimed in claim 1 which is the sodium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

5. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 4 as an active ingredient.

6. A pharmaceutical composition as claimed in claim 5 which is useful as an HMG-CoA reductase inhibitor.

7. A process for the preparation of a compound as claimed in any one of claims 1-4 which comprises

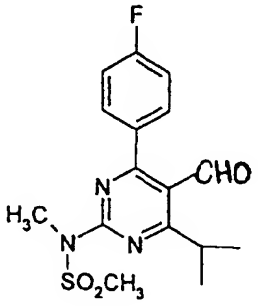
   (1) subjecting compound a



a

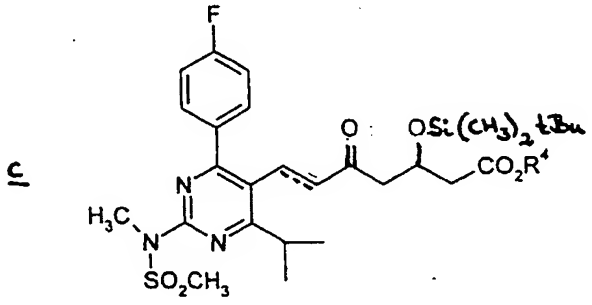
wherein Alkyl means straight, branched or cyclic C_1 to C_6 alkyl to a reduction in an appropriate inactive solvent in the presence of a reductant to give the alcohol compound,

(2) subjecting the thus obtained alcohol compound to an oxidation in an appropriate solvent in the presence of an oxidizing agent to give aldehyde compound b



b

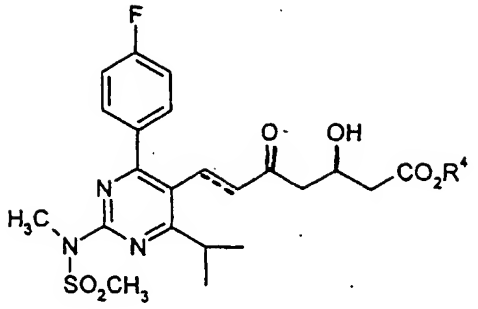
(3) which is reacted with 3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanoic acid derivatives in an appropriate solvent to give compound c



c

wherein the dotted line denotes the presence of a double bond, and R^4 is a straight, branched or cyclic C_1 to C_6 alkyl

(4) which is subjected to elimination of the tert-butyldimethylsilyl group in an appropriate organic solvent in the presence of a hydrogen halogenide to give compound d



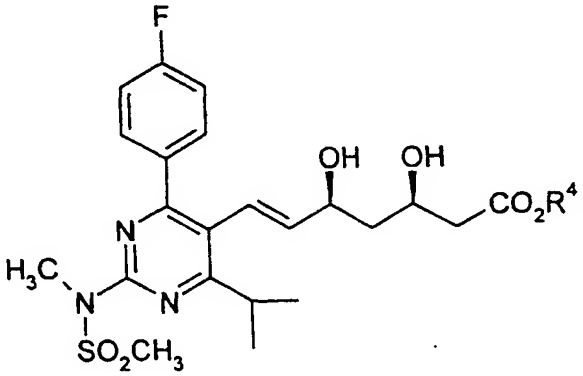
wherein the doffed line and R^4 have the same meaning as defined above

(5) which is reacted with diethylmethoxyborane and $NaBH_4$, in an alcohol-organic solvent mixture and subjected to column chromatography on silica gel and the obtained product is subjected to saponification in a polar solvent with a solution of metallic hydroxide (in the case where the desired product is a non-toxic pharmaceutically acceptable salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid or after the saponification, it is neutralized with an inorganic acid (in the case where the desired product is (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

8. A process for the preparation of a pharmaceutical composition as defined in claims 5 or 6 which comprises admixing a compound as defined in any one of claims 1 to 4 with a pharmaceutically acceptable carrier.

9. A compound as claimed in any of claims 1 to 4 for use as an active pharmaceutical substance.

10. A process for preparing a non-toxic pharmaceutically acceptable salt of the compound (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid which comprises saponification of



wherein R^4 is a straight, branched or cyclic C_1 to C_6 alkyl, in a polar solvent with a solution of a metallic hydroxide.

11. A process as claimed in claim 10, followed by neutralisation with an inorganic acid to give (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

12. A process for the preparation of the calcium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid which comprises reaction of the sodium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid with a water soluble calcium salt under aqueous conditions.

13. A process as claimed in claim 12, wherein the water soluble calcium salt is calcium chloride.

14. A process for the preparation of a pharmaceutical composition which comprises admixing the calcium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid with a pharmaceutically acceptable carrier.

15. Use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a pharmaceutical composition.

16. Use according to claim 15, wherein the pharmaceutical composition is for treating hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

Patentansprüche

1. Verbindung (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure oder ein nicht toxisches, pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, die (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl)-(3R,5S)-dihydroxy-(E)-6-heptensäure ist.

3. Verbindung nach Anspruch 1, die das Calciumsalz von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure ist.

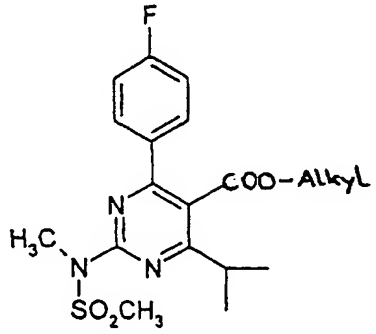
4. Verbindung nach Anspruch 1, die das Natriumsalz von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure ist.

5. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 1 bis 4 als Wirkstoff.

6. Arzneimittel nach Anspruch 5, das sich als HMG-CoA-Reduktase-Inhibitor eignet.

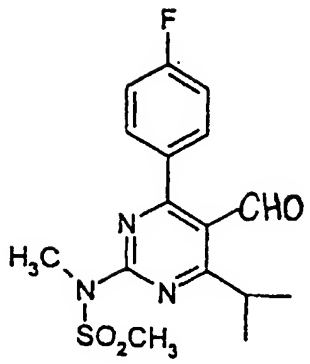
7. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 4, umfassend

(1) das Unterwerfen einer Verbindung a



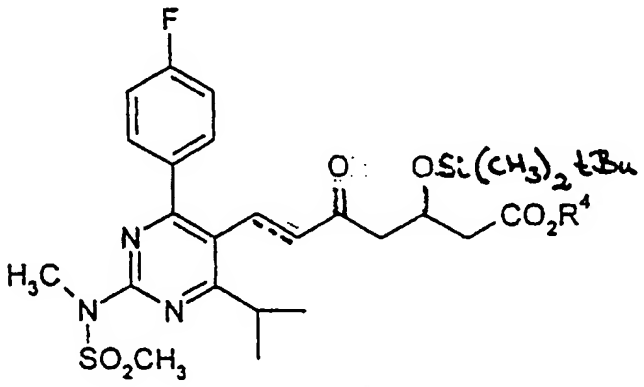
a

wobei Alkyl die Bedeutung gerader, verzweigter oder cyclischer C_1- bis C_6-Alkylrest hat,
einer Reduktion in einem geeigneten inaktiven Lösungsmittel in Anwesenheit eines Reduktionsmittels, so dass die Alkohol-Verbindung erhalten wird,
(2) Unterwerfen der so erhaltenen Alkohol-Verbindung einer Oxidation in einem geeigneten Lösungsmittel in Anwesenheit eines Oxidationsmittels, so dass die Aldehyd-Verbindung b erhalten wird



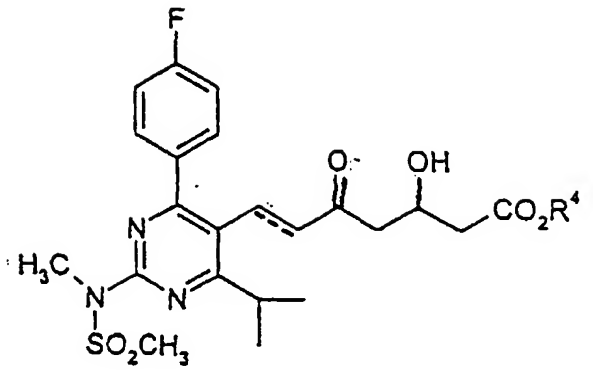
b

(3) die mit 3-(tert.-Butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidenhexansäure-Derivaten in einem geeigneten Lösungsmittel umgesetzt wird, so dass Verbindung c erhalten wird



c

wobei die gestrichelte Linie die Anwesenheit einer Doppelbindung angibt und R^4 ein gerader, verzweigter oder cyclischer C_1- bis C_6-Alkylrest ist,
(4) die einer Eliminierung der tert.-Butyldimethylsilyl-Gruppe in einem geeigneten organischen Lösungsmittel in Anwesenheit eines Halogenwasserstoffs unterworfen wird, so dass Verbindung d erhalten wird



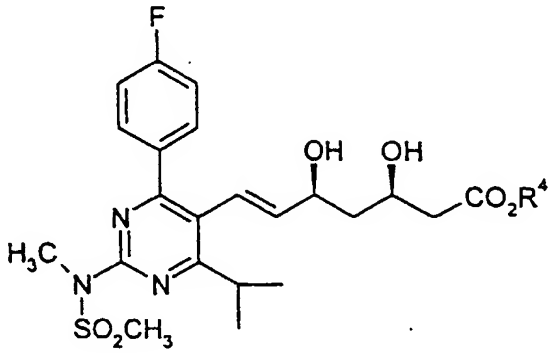
wobei die gestrichelte Linie und R^4 die gleiche Bedeutung haben, wie vorstehend definiert,

(5) die mit Diethylmethoxyboran und $NaBH_4$ in einem Gemisch aus Alkohol und organischem Lösungsmittel umgesetzt und einer Säulenchromatographie auf Silicagel unterworfen wird, und das erhaltene Produkt einer Verseifung in einem polaren Lösungsmittel mit einer Metallhydroxid-Lösung (wenn das gewünschte Produkt ein nicht toxisches, pharmazeutisch verträgliches Salz von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure ist) unterworfen wird oder nach der Verseifung mit einer anorganischen Säure neutralisiert wird (wenn das gewünschte Produkt (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure ist).

8. Verfahren zur Herstellung eines Arzneimittels wie in Anspruch 5 oder 6 definiert, umfassend das Mischen einer Verbindung nach einem der Ansprüche 1 bis 4 mit einem pharmazeutisch verträglichen Träger.

9. Verbindung nach einem der Ansprüche 1 bis 4 zur Verwendung als pharmazeutischer Wirkstoff.

10. Verfahren zur Herstellung eines nicht toxischen, pharmazeutisch verträglichen Salzes der Verbindung (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure, umfassend die Verseifung von



wobei R^4 ein gerader, verzweigter oder cyclischer C_1- bis C_6-Alkylrest ist, in einem polaren Lösungsmittel mit einer Lösung eines Metallhydroxids.

11. Verfahren nach Anspruch 10, gefolgt von der Neutralisierung mit einer anorganischen Säure, so dass (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure erhalten wird.

12. Verfahren zur Herstellung des Calciumsalzes von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure, umfassend die Umsetzung des Natriumsalzes von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure mit einem wasserlöslichen Calciumsalz unter wässrigen Bedingungen.

13. Verfahren nach Anspruch 12, wobei das wasserlösliche Calciumsalz Calciumchlorid ist.

14. Verfahren zur Herstellung eines Arzneimittels, umfassend das Mischen des Calciumsalzes von (+)-7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptensäure mit einem pharmazeutisch verträglichen Träger.

15. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels.

16. Verwendung nach Anspruch 15, wobei das Arzneimittel zur Behandlung von Hypercholesterinämie, Hyperlipoproteinämie und Atherosklerose bestimmt ist.

Revendications

1. Composé acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque ou sel non toxique pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1 qui est l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque.

3. Composé selon la revendication 1 qui est le sel de calcium de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque.

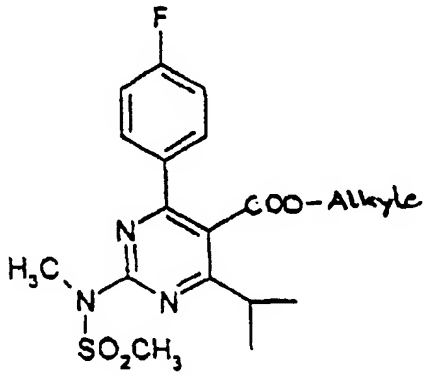
4. Composé selon la revendication 1 qui est le sel de sodium de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque.

5. Composition pharmaceutique qui comprend un composé selon l'une quelconque des revendications 1 à 4 comme ingrédient actif.

6. Composition pharmaceutique selon la revendication 5 qui est utile comme inhibiteur de la HMG-CoA réductase.

7. Procédé de préparation d'un composé selon l'une quelconque des revendications 1-4 qui comprend

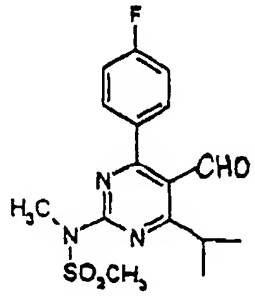
(1) la soumission du composé a



a

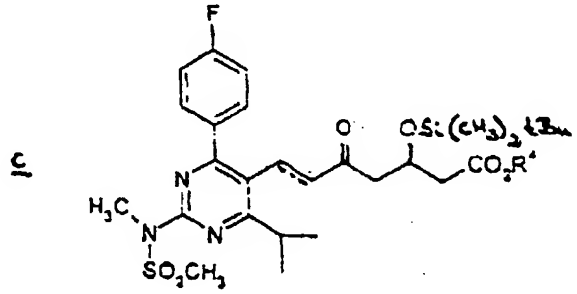
où alkyle signifie alkyle en C_1 à C_6 linéaire, ramifié ou cyclique à une réduction dans un solvant inactif approprié en présence d'un réducteur pour donner le composé alcoolique,
(2) la soumission du composé alcoolique ainsi obtenu à une oxydation dans un solvant approprié en présence

d'un agent oxydant pour donner le composé aldéhydique b



b

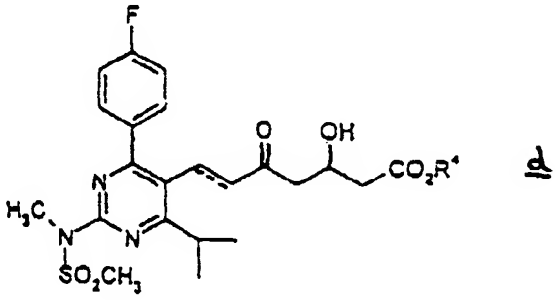
(3) qui est mis à réagir avec des dérivés de l'acide 3-(tert-butyldiméthylsilyloxy)-5-oxo-6-triphénylphosphoranilydènehexanoïque dans un solvant approprié pour donner le composé c



c

où le trait pointillé indique la présence d'une double liaison et R^4 est un alkyle en C_1 à C_6 linéaire, ramifié ou cyclique

(4) qui est soumis à l'élimination du groupe tert-butyldiméthylsilyle dans un solvant organique approprié en présence d'un halogénure d'hydrogène pour donner le composé d



d

où le trait pointillé et R^4 ont la signification définie ci-dessus

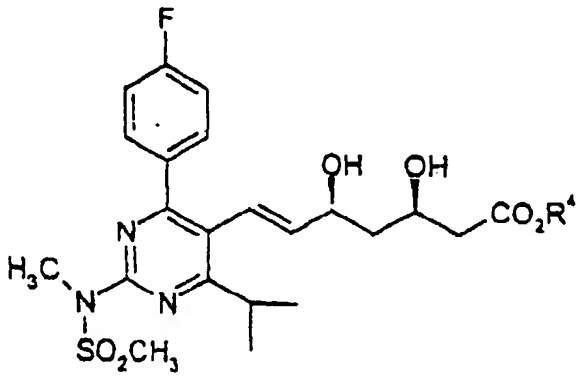
(5) qui est mis à réagir avec le diéthylméthoxyborane et $NaBH_4$, dans un mélange alcool-solvant organique et soumis à une chromatographie sur colonne sur gel de silice et le produit obtenu est soumis à une saponification dans un solvant polaire avec une solution d'hydroxyde métallique (dans le cas où le produit voulu est un sel non toxique pharmaceutiquement acceptable de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonyl amino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque) ou après la saponification, il est neutralisé avec un acide inorganique (dans le cas où le produit voulu est l'acide (+)-7-[4-(4-fluorophényl)-6-iso-

propyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque).

8. Procédé de préparation d'une composition pharmaceutique selon les revendications 5 ou 6 qui comprend le mélange d'un composé selon l'une quelconque des revendications 1 à 4 avec un véhicule pharmaceutiquement acceptable.

9. Composé selon l'une quelconque des revendications 1 à 4 destiné à être utilisé comme substance pharmaceutique active.

10. Procédé de préparation d'un sel non toxique pharmaceutiquement acceptable du composé acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque qui comprend la saponification de



où R^4 est un alkyle en C_1 à C_6 linéaire, ramifié ou cyclique, dans un solvant polaire avec une solution d'un hydroxyde métallique.

11. Procédé selon la revendication 10 suivi par la neutralisation avec un acide inorganique pour donner l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque.

12. Procédé de préparation du sel de calcium de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque qui comprend la réaction du sel de sodium de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque avec un sel de calcium hydrosoluble dans des conditions aqueuses.

13. Procédé selon la revendication 12 où le sel de calcium hydrosoluble est le chlorure de calcium.

14. Procédé de préparation d'une composition pharmaceutique qui comprend le mélange du sel de calcium de l'acide (+)-7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptènoïque avec un véhicule pharmaceutiquement acceptable.

15. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4 pour la fabrication d'une composition pharmaceutique.

16. Utilisation selon la revendication 15 où la composition pharmaceutique est destinée au traitement de l'hypercholestérolémie, de l'hyperlipoprotéinémie et de l'athérosclérose.